Claim 51 (Amended). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinantly produced *H. pylori* CT polypeptide, wherein said recombinantly produced polypeptide (i) comprises at least ten amino acids, (ii) can induce the production of antibodies to *H. pylori*, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity, and a pharmaceutically acceptable carrier.

D4 cont.

Claim 52 (Amended). The method of claim 50, wherein the second polypeptide comprises SEQ ID NO:5, or a fragment thereof, which second polypeptide: (i) comprises at least ten amino acids, (ii) can induce the production of antibodies to *H. pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

Please add new claim 53 as follows.

Claim 53 (New). The vaccine of claim 51, wherein said polypeptide comprises at least fifteen amino acids.

D5

## REMARKS

Claims 38 - 40, 42, 43, 45, 46, and 48 - 52 were pending.

Claims 39, 40, 42, 43, 45, 46, and 48 - 52 have been rejected.

By way of this amendment, claims 39, 40, 42, 43, 45, 46, and 48 - 52 are amended, and new claim 53 is introduced.

Pursuant to 37 C.F.R. §1.121(c)(1)(ii), marked up versions of claims 39, 40, 42, 43, 45, 46, and 48 - 52, showing all changes relative to the previous version of each, appear on separate sheets appended to this response.

Upon entry of this amendment claims 38 - 40, 42, 43, 45, 46, and 48 - 53 will be pending.

In view of the amendments presented herewith and the following remarks, Applicants respectfully request that the final rejection of the claims be reconsidered and withdrawn.

**Summary of the Amendment**

Claims 39, 40, 42, 43, 45, 46, 48 - 50, and 52 are amended to clarify and more accurately describe that which is claimed. Support for these amendments is found in the original claims and throughout the specification as originally filed (for example, at page 14, lines 8 - 11 and lines 24 - 27). Claim 42 is also amended in dependency to refer to a specific embodiment of the invention, support for which is found at page 14, lines 24 - 27. No new matter has been added.

New claim 53 is added for consistency and to refer to specific embodiments of the invention. Applicants believe new claim 53 adds no burden to the Examiner. Support for new claims 53 is found in the original claims, and throughout the specification as originally filed (for example, at page 14, lines 24 - 27). No new matter has been added.

**Drawings**

Pursuant to 37 C.F.R. §1.85(c), formal drawings will be filed upon a receipt of a Notice of Allowance.

**Declaration**

The Examiner stated, at page 4 of the Official Action, that no executed copy of the Declaration of Giuseppe Del Giudice ("Declaration") had yet been matched with the application. Applicants mailed the executed Declaration to the PTO on August 22, 2000. A copy of the executed Declaration is enclosed herewith. Applicants have received the return postcard that accompanied the executed Declaration to the PTO, and that postcard was stamped as received by the PTO on

August 25, 2000. A copy of this postcard is provided herewith. Applicants presume that, by now, the executed Declaration has been matched with the application, and respectfully request that the Examiner acknowledge receipt of same in response.

**Rejections under 35 U.S.C. §112, second paragraph**

The Examiner rejected claims 39, 40, 42, 43, 45, 46, 48 - 50, and 52 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention, for the recitation of the phrase "at least about." Applicants respectfully traverse this rejection.

Specifically, the Examiner questions the range of specificity of the term "about."

In the interest of advancing prosecution of the application, claims 39, 40, 42, 43, 45, 46, 48 - 50, and 52 have been amended to delete the term "about."

The Applicants respectfully request that the rejection of claims 39, 40, 42, 43, 45, 46, 48 - 50, and 52 under 35 U.S.C. §112, second paragraph be withdrawn.

**Rejections under 35 U.S.C. §112, first paragraph**

Claims 43, 45, 46, and 48 - 52 were rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement for prophylactic or therapeutic vaccines or methods of making and using such vaccines. Applicants respectfully traverse this rejection.

The enablement requirement of 35 U.S.C. §112 is satisfied if a disclosure contains sufficient information such that persons of ordinary skill in the art, having the disclosure before them, would be able to make and use the invention. The legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Applicants respectfully submit that the reasoning and evidence offered in the Official Action is insufficient to support the conclusion that the claimed invention is not enabled. Applicants

respectfully submit that one having ordinary skill in the art could practice the claimed invention without undue experimentation. Applicants respectfully submit that the requirements of the first paragraph of 35 U.S.C. §112 have been met.

At page 5 of the Official Action, the Examiner "avers to the existence of animal models for the study of *H. pylori* infection and the existence of immunological screening assays for determining immunogenic fragments." The Examiner alleges, however, that

> the existence of animal models does not in itself support Declarant's conclusion that these animal models would allow determination of prophylactic or therapeutic effect to be routinely carried out with a reasonable expectation of success.

The Examiner supports this conclusion by reference to an Exhibit, and alleging that the Exhibit, showing protection from *H. pylori* in the absence of antibodies, "contradicts Declarant's conclusion." Applicants respectfully disagree with the Examiner's reasoning. The Examiner referred to Exhibit E, which is Telford *et al.*, 1994, J. Exp. Med., 179:1653-1658. Applicants believe that the Examiner intended to refer to Exhibit F (Nedrud, 1999, *FEMS Immunol. Med. Microbiol.* 24:243-50) and will address their arguments accordingly. If Applicants' belief is incorrect, they reserve the right to respond upon clarification.

The Examiner's comments regarding §2.8.3 of Exhibit F, spanning the bottom of page 5 to the top of page 6 of the Official Action, do not negate enablement of the claimed invention. Any of numerous animal models of *H. pylori* infection that existed at the time of the earliest priority date for the present application can be used in a routine manner to evaluate the therapeutic or prophylactic efficacy of a vaccine preparation against *H. pylori* infection. The Examiner accepts the existence of such models of *H. pylori* infection, yet the Examiner fails to accept that the models could be used in a routine manner to test vaccine preparations. Applicants respectfully submit that nothing described by Exhibit F would alter the routine nature of using *H. pylori* infection models to test a candidate vaccine for its ability to prevent or treat *H. pylori* infection.

The animals used in the study described in §2.8.3 of Exhibit F were **immunodeficient** mice. Thus, that antibody-independent, protective mucosal immunity was demonstrated in that particular model has no bearing upon the general ability to evaluate a test vaccine in a model of *H. pylori* infection. These mice have no B cells and, therefore, cannot produce antibodies. Evidence of protection in the absence of antibodies in that particular model, does not preclude that protection can be elicited with an antibody response.

While acknowledging that screening for linear epitopes was routine (page 6 of the Official Action), the Examiner alleged that "discovery of the protective epitope or epitopes would still be highly unpredictable and involve extensive, undue experimentation." The Examiner's arguments were based more upon predicting which conformational epitopes are therapeutic or prophylactic. The polypeptides which are effective as vaccines, however, may comprise linear epitopes. Nevertheless, Applicants are not required to predict *a priori* which polypeptide portions or fragments of the entire CT protein will be effective in prophylactic or therapeutic vaccines before testing. Applicants only need to enable one of skill in the art to be able to identify them without undue experimentation.

Applicants submit that the application as filed enables the invention as claimed. The specification discloses the nucleotide and amino acid sequence information for *H. pylori* CT protein. Applicants have established that the generation of various polypeptides (full length and fragments) of the CT protein and the testing of these polypeptides as candidate prophylactic or therapeutic vaccines in the various animal models of *H. pylori* infection would have been routine. Applicants have effectively taught the skilled artisan how to make and use the claimed invention. The Examiner is reminded that whether or not experimentation is undue is not measured quantitatively, but qualitatively. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996); *see also Wands, supra*, 8 U.S.P.Q.2d at 1403-07.

As further support that animal models of *H. pylori* infection can be used for the testing the efficacy of vaccines comprising whole and fragments of *H. pylori* CT antigen, Applicants

submit Marchetti *et al.*, 1998, Vaccine, 16:33-7 ("Marchetti"), a copy of which is provided herein. Marchetti describes successful intragastric vaccine testing with an animal model. The focus of Marchetti was to assess the adjuvanticity of a non-toxic mutant of a mucosal adjuvant. VacA (CT) and CagA (cytotoxin associated immunodominant (CAI) antigen), and certain fragments thereof, were tested for protective efficacy in the Marchetti study.

The recombinant VacA polypeptides that were tested were TOX100, TOX37, and TOX58. The constructs that were used to produce the TOX100, TOX37, and TOX58 recombinant proteins are depicted in Figure 1 of Exhibit A (Manetti *et al.*, 1995, *Infect. Immun.* 63:4476-4480). Also shown is the construct for TOX140, which contains the entire gene for VacA. One can see that the complete VacA gene includes coding sequences for an amino-terminal signal peptide and a carboxy-terminal outer membrane exporter region. Although Marchetti designates TOX100 as the "whole recombinant VacA molecule," it is actually a polypeptide representing mature VacA, which is less than the entire cytotoxin protein encoded by the VacA gene. TOX37 and TOX58 are also fragments of VacA, representing the amino-terminal and carboxy-terminal portions of the mature VacA protein.

Applicants' specification discloses, as SEQ ID NO:3, the entire protein sequence encoded by the complete *H. pylori* cytotoxin gene (SEQ ID NO:2). Applicants' specification, at page 5, lines 31 - 35, defines the full CT protein as the full sequence shown in Figure 2 (SEQ ID NO:3), of molecular weight of about 140 kDa. Therefore, any polypeptide having a length less than the full length of SEQ ID NO:3, would be a "fragment thereof." Recombinant proteins TOX100, TOX37, and TOX58 are, therefore, fragments of *H. pylori* CT, as defined in the specification.

The TOX100 recombinant fragment yielded 33.3% protection, which was significantly enhanced by the mucosal adjuvant. Although the TOX37 and TOX58 fragments did not yield what the authors call statistically significant protection, the criteria of a protective effect was stringent. One hundred percent protection from **any** *H. pylori* growth was required. Marchetti states, at page 34, column 2, that "[m]ice were considered as 'not infected' when **no** *H. pylori* colony

was detected on the plate on which the stomach was cultured." (Emphasis supplied). A single colony, thus, was gauged as an infection. No information on the number of colonies observed was provide. Applicants' vaccine claims do not require that the protection elicited be 100%. The specification states, at page 15, lines 14 - 17

> [a] "vaccine" is an immunogenic, or otherwise capable of eliciting protection against H. pylori, whether **partial** or complete, composition useful for treatment of an individual.

(Emphasis added).

The Examiner has alleged, at page 7 of the Official Action, that Exhibit G (Ghiara *et al.*, 1997, Infect. Immun., 65:4996-5002) and Exhibit H (PCT application PCT/IB99/00851) "fail to support enablement of the claimed invention." The Examiner alleges that the references submitted by Applicants support her enablement rejection, and her conclusion that "the effects of *in vivo* administration were poorly understood until recently." Applicants respectfully disagree and submit that the claimed invention is enabled by the application as filed.

"[T]he Examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation." M.P.E.P. §2164.04. The Examiner has not specifically identified the missing information, and therefore, has not effectively disputed the objective truth of the Applicants' assertion that the invention is enabled. Instead, the Examiner has pointed generally at the alleged unpredictability of the art. "Mere broad generalizations and allegations are insufficient for holding of non-enablement." *Ex parte Goeddel*, 5 U.S.P.Q.2d 1449, 1451 (B.P.A.I. 1987).

As the Examiner has acknowledged, "these two references demonstrate the vaccine potential of the CT protein." Exhibit H was relied upon by Applicants to show that mucosal delivery and mucosal adjuvants are, in fact, not required to achieve an effective *H. pylori* vaccine, and to refute the Examiner's assertion, at page 3 of the prior Official Action of February 7, 2000, "that a

mucosal adjuvant is required for vaccine efficacy." Exhibit G was relied upon by Applicants to show that vaccines comprising CT polypeptides can have a therapeutic, as well as protective effect.

Evidence that certain assumptions about the role of gastric antibodies were incorrect does not negate the ability of one skilled in the art to use *H. pylori* infection models to test candidate vaccines. In fact, such evidence supports enablement. As the Examiner acknowledges, Exhibit H indicates that a "systemic" protective effect can be achieved, and confirms that mucosal adjuvants are not necessary.

The Examiner has alleged (page 6) that Exhibits G and H, as "post-filing documents cannot support enablement of a claimed invention unless the teachings of these documents follow the teachings of the specification." Applicants respectfully submit that it is well settled that while "a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling," it can be "offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative." *Gould v. Quigg*, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987). Applicants do not seek to describe techniques and materials not described in the specification. Applicants submit that the claimed invention is enabled by the specification as filed. Exhibits G and H support operability of the claimed invention using no new techniques or materials beyond what was generally known to the art or disclosed in Applicants' specification at the time of filing.

Applicants respectfully urge the Examiner to reconsider her position and recognize that one skilled in the art could practice the claimed invention based upon the original disclosure. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43, 45, 46, and 48 - 52 under 35 U.S.C. §112, first paragraph.

## Conclusion

Applicants respectfully submit that claims 38 - 40, 42, 43, 45, 46, and 48 - 54 are in condition for allowance. A notice of allowance is earnestly solicited. If the Examiner feels a telephonic interview would be helpful, she is asked to call the undersigned at 215-557-5901.

## Correspondence

Applicants hereby inform the Examiner that a Change of Correspondence Address for this application has been filed on November 21, 2000. All correspondence from the Patent and Trademark Office concerning this application should be sent to:

Alisa A. Harbin, Esq.
Vice President & Associate Chief Patent Counsel
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94608-8097

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Date: March 7, 2001

**Robin S. Quartin**
Registration No. **45,028**

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Attachments:
marked up versions of amended claims 39, 40, 42, 43, 45, 46, and 48 - 52

Enclosures:
copy of Marchetti *et al.* (1998) *Vaccine* 16:33-7
copy of executed Declaration of Giuseppe Del Giudice
copy of return postcard stamped August 25, 2000

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**Marked up versions of claims 39, 40, 42, 43, 45, 46, and 48 - 52, which are amended herein, showing all of the changes relative to the previous version of each.**

**In the claims:**

Claim 39 (Twice amended). A recombinantly produced [fragment of a *Helicobacter*] H. pylori CT polypeptide, wherein the recombinantly produced [fragment] polypeptide (i) comprises at least [about] ten amino acids, (ii) can induce the production of antibodies to [*Helicobacter*] *H. pylori*, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity.

Claim 40 (Twice amended). A recombinantly produced *H. pylori* CT polypeptide [or fragment thereof] comprising SEQ ID NO:3 or a fragment thereof, which polypeptide or fragment thereof : (i) comprises at least [about] ten amino acids of SEQ ID NO:3, (ii) can induce the production of antibodies to [*Helicobacter*] *H. pylori*, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity.

Claim 42 (Twice amended). The polypeptide of [claim] either of claims 39 or 40, wherein said polypeptide comprises at least [about] fifteen amino acids.

Claim 43 (Twice amended). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a *H. pylori* CT polypeptide comprising SEQ ID

NO:3 or a fragment thereof, which polypeptide: (i) comprises at least [about] ten amino acids of SEQ ID NO:3, (ii) can induce the production of antibodies to [*Helicobacter*] <u>*H. pylori*</u>, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity.

Claim 45 (Twice amended). The vaccine of claim 43, wherein said polypeptide comprises at least [about] fifteen amino acids.

Claim 46 (Twice amended). The vaccine of claim 43, further comprising an immunologically effective amount of a second polypeptide comprising *H. pylori* cytotoxin associated immunodominant (CAI) antigen or a fragment thereof, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can induce the production of antibodies to [*Helicobacter*] <u>*H. pylori*</u>, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

Claim 48 (Twice amended). The vaccine of claim 46, wherein said second polypeptide comprises at least [about] fifteen amino acids.

Claim 49 (Twice amended). A method of preparing a prophylactic or therapeutic vaccine comprising bringing into association:

(1) an immunologically effective amount of a *H. pylori* CT polypeptide, which polypeptide: (i) comprises at least [about] ten amino acids, (ii) [*Helicobacter*] <u>*H. pylori*</u>, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity, and

(2) a pharmaceutically acceptable carrier.

Claim 50 (Twice amended). The method of claim 49, further comprising adding an immunologically effective amount of a second polypeptide comprising *H. pylori* CAI antigen or fragment thereof, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can induce the production of antibodies to [*Helicobacter*] H. *pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

Claim 51 (Amended). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinantly produced *H. pylori* CT polypeptide, wherein said recombinantly produced polypeptide (i) comprises at least ten amino acids, (ii) can induce the production of antibodies to *H. pylori*, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity, and a pharmaceutically acceptable carrier.

Claim 52 (Amended). The method of claim 50, wherein the second polypeptide comprises SEQ ID NO:5, or a fragment thereof, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can induce the production of antibodies to [*Helicobacter*] H. *pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

New Claim 53 has been added.